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Disease-a-Month

Hypothyroidism

SIDNEY H. INGBAR
NORBERT FREINKEL

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Hypothyroidism

SIDNEY H. INGBAR
NORBERT FREINKEL

TABLE OF CONTENTS

Metabolism of Thyroid Hormone 4

Mechanism of Thyroid Hormone Action 6

Thyroid Hormone Role in Intermediate Metabolism 8
- Metabolism of Salt and Water 8
- Metabolism of Carbohydrates 10
- Metabolism of Proteins 11
- Metabolism of Lipids 11
- Metabolism of Vitamins 12
- Metabolism of Endocrine Structures 13

Systemic Changes in Myxedema 15
- Integumentary System 15
- Cardiovascular System 16
- Gastrointestinal System 19
- Reproductive System 19
- Muscular System 20
- Skeletal System 21
- Hematopoietic System 22
- Central Nervous System and Psyche 23

Etiologic Classification 24
- Nongoitrous Hypothyroidism 25
- Goitrous Hypothyroidism 30

Laboratory Findings 35

Clinical Use of Thyroid-Stimulating Hormone 37
- Differentiation of Thyroidal and Pituitary Myxedema . . . 37
- Diagnosis of Hypothyroidism in the Treated Patient . . . 38
- Diagnosis of Hypothyroidism in Patients Receiving Iodide . . 38
- Diagnosis of Decreased Thyroid Reserve 38

Treatment 39

Metabolic Insufficiency 42

Sidney H. Ingbar

is Assistant Physician, Thorndike Memorial Laboratory, Assistant Professor of Medicine, Harvard Medical School and Investigator, Howard Hughes Medical Institute. Dr. Ingbar spent a year in biochemical research at the National Institute for Medical Research, London, England. He received his M.D. degree from Harvard University and interned at Boston City Hospital. His main interests are internal medicine, endocrinology and intermediate metabolism.

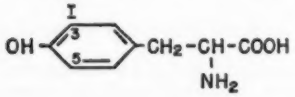
Norbert Freinkel

is a graduate of New York University College of Medicine, was intern and assistant resident, III Medical Division, Bellevue Hospital, New York. Since 1952, Dr. Freinkel has been at Thorndike Memorial Laboratory, with the exception of a year spent in biochemical research in Cambridge, England. He is currently Assistant Physician, Thorndike Memorial Laboratory, Investigator, Howard Hughes Medical Institute and Associate in Medicine, Harvard Medical School. His interests also are internal medicine, endocrinology and intermediate metabolism.

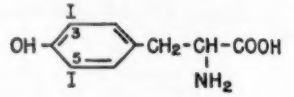
IN MAN, as in all vertebrate species, failure to meet the requirements of tissues for thyroid hormone results in multiple derangements of function and development. The resultant clinical entity has been called hypothyroidism. This designation, with the primary emphasis on the thyroid gland, is a misnomer. Although a lack of thyroid hormone can be attributed most commonly to an insufficient elaboration of glandular products, biosynthetic failure may be accompanied by glandular hyperfunction as well as hypofunction. Throughout this review, we will use the term hypothyroidism, in accord with common usage. However, we stress that the syndrome under discussion is a consequence of a peripheral lack of thyroid hormone rather than of disease within the thyroid gland per se. Thus, at the outset, it may be germane to review the metabolism and actions of thyroid hormone.

METABOLISM OF THYROID HORMONE

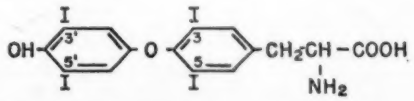
Thyroxin (T_4, see illustration) constitutes the principal hormonal elaboration of the thyroid gland. The early indirect



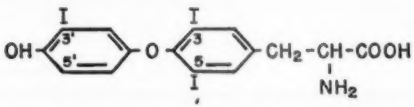
3-MONOIODOTYROSINE



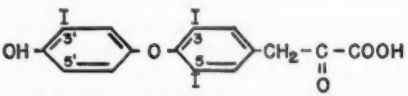
3,5-DI-IODOTYROSINE



3,5,3',5'-TETRAIODOTHYRONINE (Thyroxin, T_4)



3,5,3'-TRI-IODOTHYRONINE (T_3)



3,5,3'-TRI-IODOTHYROPYRUVIC ACID

Representative iodinated compounds of biologic interest in the study of hypothyroidism and its causes.

evidence based on analysis of peripheral blood (73) has been documented recently by direct characterization of the thyroidal venous effluent (74). Small amounts of triiodothyronine (T_3 in illustration) can also be demonstrated in thyroid vein blood, but thyroglobulin and iodinated tyrosines are not normally released into the blood stream. Circulating thyroxin is associated

with the plasma proteins, chiefly with a specific alpha globulin, which has been called the thyroxin-binding protein (TBP) (25). Circulating triiodothyronine is more loosely bound to the plasma proteins and is associated with components other than the specific TBP. In euthyroid persons, the virtual volume of distribution of extrathyroidal thyroxin is equal to about 15% of body weight (34). Thyroxin is removed from this "thyroxin space" at a fractional turnover rate of about 10% daily so that, under conditions of normal homeostasis, about half the extrathyroidal thyroxin is renewed every 7 days (34). In contrast, the less tightly bound triiodothyronine is distributed in a volume that approximates 30-40% of body weight and is removed from the "triiodothyronine space" at a rate of about 30% daily (69).

Relative intercomparisons of the peripheral blood levels of thyroxin and triiodothyronine must take into account the larger volume of distribution and the more rapid turnover of the latter. However, even when all these aspects are considered, it can be shown that triiodothyronine does not constitute an appreciable proportion of the thyroid hormone delivered to the tissues. The determinants of the transcellular flux of thyroid hormone have not been elucidated fully. Various possibilities have been outlined in a recent discussion (22). It is becoming increasingly apparent that protein-binding phenomena may be important in delimiting the exchange of thyroidal hormones between cellular and extracellular phases.

Pathways for the disposition of both T_3 and T_4 have been reviewed by Berson (9). Urinary excretion accounts for negligible losses except in the presence of proteinuria. In man, in contradistinction to the rat, only a small proportion of extrathyroidal hormone enters the enterohepatic circulation. Some of this is conjugated with glucuronic acid and subsequently hydrolyzed in the intestinal tract and reabsorbed. The balance, not exceeding 10-20% of the daily loss of thyroid hormone, is excreted as hormonal iodine in the feces. By far, the greatest removal of extrathyroidal thyroid hormone occurs at the tissue level. Here, both in vivo and in vitro, iodine is split off the thyronine residue and rendered available as ionic iodide for urinary excretion or for thyroidal reaccumulation. The recent demonstration of the acetic and pyruvic acid derivatives of thyroxin and triiodothyronine (52) would suggest that oxidative deamination and decarboxylation of the alanine side chain may precede deiodination of the diphenyl ether nucleus under certain con-

ditions. In this regard, the metabolic fate of the thyronine derivatives would not be different from that of other amino acids.

Following the administration of thyroxin to thyroprival subjects, there is a lag of at least 6 hours before the onset of hormonal action. The lag phase is appreciably shortened when triiodothyronine is given. The heightened and accelerated response to the metabolic products of thyroxin degradation has evoked much literature suggesting that thyroxin must be converted to an active form before it can exert hormonal action. As yet, no definitive data support this thesis, first advanced by Gross and Pitt-Rivers (27). To date, conclusive evidence has not been forthcoming that hormonal action and hormonal degradation are more than fortuitously related. Indeed, it is conceivable that the differences between thyroxin and the other compounds (64) may merely reflect variation in affinities for protein binding. Thus, the less tightly bound derivatives would be more readily available for cellular delivery and for consequent hormonal action. Definitive evaluation of this and other possibilities awaits an in vitro cellular system wherein hormonal action can be achieved and extracellular binding components can be excluded.

MECHANISM OF THYROID HORMONE ACTION

For thyroid hormone, the precise end-organs, the intracellular localization and the mechanism of hormone action have not been defined. It has long been known that the administration of thyroidal extracts to athyreotic subjects is followed by an augmented utilization of oxygen and an enhanced liberation of heat. These phenomena are independent of the nervous system, for they can be elicited in denervated structures. Furthermore, they do not require sustained vascular perfusion, for they persist in isolated tissues obtained after the administration of thyroid hormone in vivo. Attempts to localize the hormone to an anatomic site within the cell have been unrewarding. Preferential accumulation of I^{131}-labeled thyroxin in the nuclear, mitochondrial, microsomal or soluble fractions of rat liver homogenates has not been observed (44, 71). A possible concentration at cellular or subcellular membrane barriers cannot be excluded from available data.

Within the cell, the energy transformations which thyroid hormone induces could, conceivably, be effected by any of several mechanisms. An action of thyroid hormone as a specific

cofactor seems unlikely, since maintenance requirements for substitution therapy are "far less than that of any of the well-established cofactors" (6). Moreover, in complete athyreosis, existing functions are only retarded, not abolished. Therapy with thyroid hormone increases the activities of certain specific enzymes (e.g., cytochrome oxidase, succinoxidase, arginase, xanthine oxidase, etc.) as summarized by Barker (6). However, the ubiquitous and nonsystematized nature of these changes would suggest that they are secondary rather than primary hormonal effects. More recently, the growing awareness that high-energy phosphate bonds constitute the energy currency of the cell has stimulated efforts to relate the action of thyroid hormone to oxidative phosphorylations. Martius (50), Lardy (43) and Niemeyer (53) and their co-workers have reported an uncoupling of oxidative phosphorylations in subcellular preparations obtained from thyroid-treated animals. Under certain conditions, these authors also have been able to dissociate oxidation from phosphorylation by the direct addition of T_3 and T_4 to mitochondria in vitro. That a direct action on complex enzyme systems, such as oxidative phosphorylation, may not be the primary event has been suggested by Tapley, Cooper and Lehninger (72). They have advanced the challenging thesis that oxidative phosphorylations are altered by thyroid hormone because of changes in the permeability and hydration of mitochondria. In this latter regard, they have shown that T_3 and T_4 differ from such agents as dinitrophenol which do not correct myxedema but which are also calorigenic and uncouple oxidative phosphorylations.

Although none of these aspects has been elucidated, it is clear that the action of thyroid hormone results in an increased generation of energy. What are the physiologic ends that the energy subserves? The early explanation of Kendall (37) still seems attractive today. He proposed that thyroid hormone does not initiate events *de novo* but rather exaggerates normal cellular activities. Within this framework, it might be anticipated that deficiency of thyroid hormone results in generalized aberrations of intermediate metabolism and focal disturbances conditioned by the functional, developmental and metabolic peculiarities of a given tissue. It is proposed to examine the more generalized phenomena preparatory to focusing on their modifications in isolated areas. No disease complex affords a more fertile ground for the correlation of clinical signs and symptoms with pathophysiology.

THYROID HORMONE ROLE IN INTERMEDIATE METABOLISM

Metabolism of Salt and Water

The internal and external environment of the cell is principally water. Cellular activities can be modified by alterations in the abundance and the distribution of this water as well as by its solute content. At the same time, it is now known that changes in cellular metabolic activity per se can affect the distribution of water and the partition of solutes between cellular and extracellular phases. In this vicious cycle, it is hard to dissociate cause and effect, but thyroid hormone is important in all aspects.

Total body water is increased in the absence of thyroid hormone (81). Body water exchanges are geared at a low level. Diuresis following a water load is delayed, insensible pulmonary losses of water are diminished and percutaneous evaporation of water is decreased to an even greater extent than is the BMR. By dye technics, it has been demonstrated that plasma volume is contracted (75) and on the basis of the dilution of thiocyanate and radioactive sodium (1) it has been reported that extracellular fluid volume is increased. The latter measurements must be interpreted with caution, since thiocyanate and sodium are not wholly excluded from the cell even under conditions of cellular eumetabolism. However, localized expansions of extracellular fluid do occur, as suggested by the relative clinical frequency of pleural and pericardial effusions and the occasional occurrence of ascites. Both the distribution and the solute compositions of the various body fluids are altered in hypothyroidism. Although serum electrolyte values are normal, the observations with thiocyanate and radioactive sodium would indicate that total body stores of sodium and chloride are augmented. The concentration of serum proteins is elevated notably in the beta globulin fraction (48). Of interest is the recent finding that the depressed level of circulating hormone is accompanied by a significant increase in the concentration of the TBP of the plasma (57).

The myxomatous character of the extravascular, extracellular fluids, rich in protein (11), and acid mucopolysaccharides (80) prompted Ord in 1878 to assign the name "myxoedema" to the condition resulting from deficient elaboration of thyroid hormone. Normally, the architectural framework of cellular structures is provided by a viscous ground substance containing chondroitin sulfate and hyaluronic acid. In myxedema, as in

fetal life, the interstitial concentration of these components is increased. Because of the curious parallel between myxedema and fetal life, Byrom (11) and Means (51) have suggested that one of the developmental functions of thyroid hormone may be to provide cells with a more mature environment. Representative samples of extracellular fluid in myxedema reflect the mucinous changes. Thus, a marked increase in the mucin nitrogen of synovial fluid has been reported, and salivary secretions in myxedema are characteristically viscid and thick. Perhaps as a consequence of the hydrophilic properties of the abundant interstitial macromolecules, the intercellular spaces are infiltrated with fluid, and cellular contiguity is disrupted.

Transcapillary and transcellular exchanges in myxedema have been inadequately documented. In myxedema, mild albuminuria is occasionally present. Elevation of the protein content of the CSF is an almost invariable finding (76). The latter may, on occasion, be as high as 200 mg.%. Although the phenomena have been attributed to increased capillary permeability, alternative explanations may be invoked. For the kidney, it has been shown that both glomerular filtration rates and renal blood flow are reduced in myxedema (14, 31).

Within recent years, evidence has accrued indicating that the establishment and maintenance of concentration differentials for solutes between cellular and extracellular phases require the continued expenditure of energy derived from cellular metabolic activities. Few discrete transport functions have been studied in myxedema. However, such scattered observations as the high incidence of gastric achlorhydria (68), the retarded intestinal absorption of glucose (2) and the depressed values for the renal tubular transport maxima for Diodrast® (14), and p-aminohippuric acid (31), would suggest that metabolically dependent transport mechanisms are widely depressed in myxedema. It is possible that derangements in transport may constitute one of the primary defects in myxedema. Certainly, failures in the transport of electrolytes could occasion drastic relocations of fluids. For example, in surviving tissue slices any impairment of oxidative cellular metabolism results in an egress of cellular potassium and an inward flow of sodium. The sodium flux is accompanied by an increase in cellular water, which, according to some, is merely a passive consequence of the entry of sodium. Thus, by extrapolation to events in vivo, it is conceivable that significant portions of the increased exchangeable sodium in myxedema may be distributed within the intracellular fluids

and that total intracellular water is augmented *pari passu*. Alternatively, the excess salt and water could be complexed with the interstitial mucopolysaccharides in slowly exchanging colloidal aggregates. Obviously there is critical need for more detailed studies of both fluid and electrolyte exchanges in myxedema, and the effects of such phenomena on intracellular metabolic activities.

Clinical findings must be projected against the foregoing considerations. Peripheral edema was present in 55% of the 77 cases of myxedema compiled by Lerman (45). Facial and palpebral edema were even more common, occurring in 79 and 90%, of these cases respectively. In almost half of edematous patients, especially early in the course of myxedema, the edema is nonpitting.

The occurrence of diuresis following the inception of therapy with thyroid hormone has been known since 1891. Occasionally, diuresis is preceded by an exacerbation of the edema. That this reflects an expansion of extracellular fluid has been demonstrated recently (81). The diuresis may be partly attributed to increased renal function. Heightened adrenal cortical activity may be contributory also. The source of mobilized fluids is less clearly defined. Urinary hexosamine rises (81) and the diuresed fluids are rich in nitrogen and phosphorus, as might be anticipated from the proteinic nature of the interstitial fluids. Sodium constitutes the principal cation, and Byrom (11) has viewed this as evidence for the extracellular origin of the fluids. Some of our recent unpublished studies have shown that serum sodium rises and the hematocrit falls just before the initiation of diuresis. At present, we cannot determine whether this results from a liberation of bound salt and water due to the breakdown of myxomatous infiltrates, from an extrusion of saline from intracellular confines or from a combination of both.

Metabolism of Carbohydrates

Myxedema is not accompanied by extreme changes in carbohydrate metabolism. The occasional occurrence of fasting hypoglycemia should arouse suspicion of a pituitary basis for the thyroidal failure. Most commonly, tests of glucose tolerance are normal. Because of delayed absorption of hexoses, oral glucose tolerance tests occasionally may be flattened. In some subjects, tolerance to intravenous glucose may be decreased also. This failure in the peripheral disposition of glucose results

from the generalized reduction in assimilative processes. There is no evidence that the proportionate disposition of carbohydrates or the metabolic mixture is altered in the absence of thyroid hormone.

Withdrawal of thyroid medication from subtotally pancreatectomized dogs results in an improvement in diabetes. Comparable findings have been reported in human diabetes. Requirements for insulin are usually diminished coincident with the development of hypothyroidism. Some amelioration may result from a retarded degradation of insulin. However, reduction in gluconeogenesis and diminution in food intake are also contributory.

Metabolism of Proteins

The delayed osseous and structural development of myxedematous children and the integumentary defects in hypothyroid adults attest to the importance of thyroid hormone in protein metabolism. The interrelations are complex. The elaboration of growth hormone by the pituitary and the peripheral action of growth hormone are impaired in the absence of adequate supplies of thyroid hormone (21). Thus, some of the growth effects of thyroid hormone may be mediated by pituitary factors. However, in addition to its synergism with growth hormone, thyroid hormone exerts certain independent actions on protein metabolism. Total exchangeable albumin is increased in myxedema: the normal distribution is reversed, so that extravascular stores of albumin exceed the intravascular and the fractional rate of albumin degradation is reduced (47). In eviscerated rats, the rise in the amino acid content of the blood may be taken as an index of protein catabolism. Thyroidectomy retards this phenomenon (10). Other investigations would indicate that anabolism of proteins, as well as catabolism, is reduced in the absence of thyroid hormone. Thus, there is a measurable diminution in the incorporation of labeled amino acids into the proteins of thyroidectomized rats (32) and myxedematous humans (16). The composite consequence of balanced defects in synthesis and degradation is a generalized slowing of protein turnover.

Metabolism of Lipids

For lipids, as with the other metabolites discussed here, thy-

roid hormone does not alter the qualitative interrelations but rather affects quantitative aspects of their metabolism. Contrary to lay opinion, obesity is uncommon in myxedema. This is because appetite usually declines commensurate with the BMR. However, if normal dietary intake is maintained, the diminished expenditure of calories for other metabolic activities results in an increased availability of nutrients for lipogenesis. In terminal myxedema, anorexia may be so profound as to result in marked inanition and depletion of body fat stores.

The most striking changes in lipids occur in the blood. Elevations of serum cholesterol have long been considered a hallmark of the myxedematous state. However, preoccupation with cholesterol may obscure the important fact that all plasma lipids, except neutral fat, are increased. Moreover, in uncomplicated myxedema, the gross interrelations of plasma lipids are preserved so that ratios of free:total cholesterol and the relations between free cholesterol and total lipid phosphorus do not depart from normal (55). By ultracentrifugal technics, elevations in the beta lipoproteins and the faster-rising lipoprotein moieties have been reported more recently (36).

Hypercholesterolemia need not be present invariably. Recent isotopic studies would tend to clarify the relations. In rats, the availability of thyroid hormone dictates the rates of hepatic cholesterol synthesis as well as the rates of cholesterol degradation and excretion (58). In the absence of thyroid hormone, all parameters are depressed; however, degradation and excretion are reduced more than synthesis (58). Thus, a transient disequilibrium ensues and serum cholesterol rises until the establishment of a new "steady state." In such a dynamic situation, the degree of hypercholesterolemia obviously will be conditioned by the magnitude of disparity between anabolic and catabolic functions.

Metabolism of Vitamins

Disorders in the metabolism of B complex vitamins have not been reported in myxedema. The sporadic association of myxedema and pernicious anemia has been attributed to fortuitous coincidence (12). Increased urinary excretion of vitamin C has been observed and may indicate a diminished requirement for this vitamin. The most striking changes have been described in the metabolism of the fat-soluble vitamins. Serum levels of tocopherol are elevated in myxedematous humans, generally

paralleling the alterations in cholesterol level (56). At present, the physiologic implications of this observation are not clear. The increment in circulating tocopherol may merely constitute another reflection of diminished lipid turnover. The disturbances in the metabolism of vitamin A are more clearly defined. Myxedema in man, as in experimental animals, is accompanied by an impaired oxidative conversion of carotene to vitamin A. Thus, serum levels of carotene are characteristically elevated and levels of vitamin A are depressed. The carotenemia may be sufficient to account for the icteric tint occasionally seen in myxedematous subjects (20). Whether thyroid hormone affects the intestinal absorption of carotene in man is still a matter of conjecture. In certain species, this may be the case, since the fecal excretion of carotene is elevated in the absence of thyroid hormone.

Metabolism of Endocrine Structures

Effects of hypothyroidism on endocrine interrelations must be viewed from two aspects: (1) the modification of hormonal synthesis due to myxedema of endocrine glands and (2) the modification of peripheral hormonal requirements and hormonal action due to myxedema of peripheral tissues. In the former, the pituitary theoretically should be more vulnerable to a deprivation of thyroid hormone than any other endocrine structure. It is one of the most active sites of protein synthesis within the body, and trophic hormones constitute products of this anabolic activity.

There is much data to suggest that the pituitary elaboration of certain trophic hormones is reduced in primary myxedema. We have already mentioned the evidence for a diminished production of growth hormone. Similar findings have been reported for the gonadotrophins. Although most myxedematous males and premenopausal females excrete normal quantities of FSH in the urine, postmenopausal females with myxedema do not exhibit as much of an elevation in the urinary output of FSH as their euthyroid counterparts (7, 78).

Direct measurements of ACTH elaboration have not been performed. However, the urinary excretion of adrenocortical products is diminished in almost all cases of primary myxedema. Reduced values have been reported for urinary 17-ketosteroids (7, 82) and 17-hydroxycorticosteroids (46). By administering ACTH exogenously to patients with myxedema,

it has been shown that normal adrenal responsivity is retained (82) and that the apparent hypofunction of the adrenal may be attributed to reduced stimulation with endogenous ACTH rather than myxedema of the adrenal gland. Clinically, there is eucorticism. Subjects with primary myxedema tolerate fasting well and manifest neither inordinate sensitivity to insulin nor hypoglycemic unresponsiveness. Their delayed excretion of water loads is not improved with cortisone but rather requires therapy with desiccated thyroid for correction. The seeming paradox of diminished adrenal synthesis of hormone and clinical eucorticism has been clarified recently. In patients with myxedema, the removal of infused adrenal steroids from the circulation is retarded. Therefore, as a result of a balanced interplay of diminished synthesis of hormone and reduced degradation of hormone, normal plasma levels of 17-hydroxycorticosteroids are maintained (46, 82). The foregoing has been considered in some detail because of a prevailing belief that myxedema is accompanied by hypoadrenocorticism. We are skeptical about this. Whether the diminished turnover of adrenal hormone is a consequence of a myxedematous pituitary gland or whether it represents a physiologic adjustment of the pituitary-adrenal axis to decreased peripheral demands cannot be stated. Most likely, both conditions obtain. That the elaboration of ACTH by the pituitary is adequate for the demands of the myxedematous state is corroborated by clinical experience. It still must be proved that myxedema of the pituitary gland may so reduce pituitary reserves as to preclude a rapid augmentation of ACTH output. Obviously, similar considerations also may pertain to the other trophic hormones elaborated in reduced amounts in myxedema.

Does myxedema of peripheral tissues alter their responsiveness to the action of hormones? This question has received recent attention in our laboratory. Kumagai has demonstrated that significant and sustained reductions in total circulating lymphocytes and eosinophils can be achieved in myxedematous subjects with one third to one quarter of the amount of infused hydrocortisone required for comparable effects in eumetabolic subjects. Dowling has shown that when postmenopausal females are given a standard amount of oral estrogen therapy, full vaginal cornification is achieved more rapidly in myxedematous than in euthyroid women. Thus, both for adrenal oxysteroids and for estrogens, the effects on peripheral tissues seem to vary inversely with cellular oxidative metabolism, and sensitivity to

exogenous hormone is enhanced in the myxedematous state. At present, we cannot say whether these phenomena reflect intrinsic changes in cellular responsiveness or whether they result merely from a prolonged availability of steroids due to retarded degradation. However, from the data, it may be inferred that less endogenous biosynthesis of hormone is required to achieve given hormonal actions in hypothyroid subjects.

SYSTEMIC CHANGES IN MYXEDEMA

Integumentary System

The myriad alterations in intermediate metabolism just discussed are nowhere expressed more manifestly than in the integumentary structures. The subepidermal infiltration with mucinous interstitial fluids and the increased water content impart to the skin a thickened, swollen, inelastic consistency. Facial features are coarsened, nasolabial folds may be accentuated and pendulous infra-orbital deposits may produce prominent pouches under the eyes. Mucous membranes also may become involved in the infiltrative process and swelling of the tongue, uvula and nasolaryngeal passages may produce speech difficulties. Activity of sweat and sebaceous glands is markedly reduced. Consequently, the skin is coarse and dry. Hyperkeratotic changes ensue and desquamation may be sufficiently pronounced to simulate ichthyosis. Hyperkeratotic plugging of hair follicles is common. Elaboration of cerumen is reduced. In the series of Lerman (45), skin changes constituted the most common objective clinical finding of myxedema, and dryness and coarseness occurred in 97% of patients. Early in myxedema, alterations in the consistency of the skin may be confined to exposed articular surfaces such as the elbows. Eventually, there is more widespread involvement. Coarseness of the dorsa of the hands may be produced by too many adventitious factors to be of much diagnostic significance. Skin changes in unexposed, indifferent areas, such as on the inner forearms and thighs, are more valuable.

The skin is characteristically cold, thus reflecting the same impairment in calorigenesis that accounts for the frequent subjective sensations of cold and the common reduction of rectal temperatures to subnormal levels in myxedematous subjects. Skin pallor is disproportionate to the changes in hemoglobin levels. Some of the pallor may result from diminished cutane-

ous blood flow. The subepidermal mucinous infiltrates also may impair light reflection from vascular structures and thus may accentuate pallor. Slight yellow pigmentation of the skin (xanthosis cutis), which occurs in many myxedematous subjects, has been attributed to a high incidence of carotenemia. Total subcutaneous stores of adipose tissue may be reduced. Focal redistributions of fat, especially increases in the supraclavicular fat pads, are common.

Diminished protein anabolism may be invoked to explain the impaired wound healing seen in myxedema. It also accounts for many integumentary changes. Growth of hair and nails is reduced. Nails are brittle, exhibiting longitudinal and transverse striations as well as lunular defects. Haircuts are needed less frequently, and in male thyroprivics, the beard is sparse, with longer intervals between shaving. Scattered zones of alopecia occur, especially on the frontal areas of the scalp. Loss of hair from the outer third of the eyebrows is especially common, although by no means pathognomonic for myxedema. The hair is coarse, dry and brittle and may break easily. Axillary and pubic hair is reduced. When deficiency of thyroid hormone occurs during intrauterine life, abnormal persistence of lanugo hair may be observed. Hirsutism occurring in infant thyroid insufficiency has been described.

Cardiovascular System

The cardiovascular adjustments to myxedema may arise centrally, from myxedema of the heart, and peripherally, from diminished metabolic demands of the myxedematous tissue. It is proposed to analyze the phenomena separately although such a dissociation may be artificial.

The term "myxedema heart" was introduced in 1918 by Zondek to connote a distinct clinical entity characterized by symmetrical cardiac dilatation, indolent heart action and electrocardiographic changes, and by prompt reversal of the abnormalities following the institution of replacement therapy with thyroid extract. Subsequent clinical experience has confirmed his observations. Enlargement of the cardiac silhouette is present in more than two thirds of myxedematous subjects. The muffled, distant quality of the heart sounds and of the apical impulse are almost invariable findings. Low-voltage, small P waves and flattening or inversion of T waves may be seen in electrocardiograms; prolongation of the P-R interval

can occur. The changes in T waves are the most frequent electrocardiographic finding. The heart rate may be slow or normal. Arrhythmias are sufficiently rare to arouse suspicion as to the presence of other coexisting cardiac disease. The incidence of pericardial effusions in myxedema is greater than is commonly appreciated. The effusions develop slowly, are rich in protein and do not occasion sufficient cardiac embarrassment to justify the hazards of pericardicentesis.

The pathophysiologic basis for "myxedema heart" has not been resolved. That mucinous infiltrations and edema can occur within the myocardia of experimentally hypothyroid animals seems reasonably well documented. The evidence for comparable histologic alterations in human myxedema is more tenuous. Thus, there are some who would attribute all the findings to the frequent pericardial effusions, since the increases in cardiac diameter, distant heart sounds and electrocardiographic changes can be reproduced by the simple instillation of saline into the pericardium. Alternatively, it has been proposed that cardiac dilatation, decreased contractile amplitude and hypotonia result from derangements in the intermediate metabolism of cardiac musculature and that, in this regard, the myocardium does not differ from other muscles of the myxedematous subject. It is likely that both factors are operative. Fluoroscopy does not aid in differentiating between the two possibilities.

The abnormalities of the "myxedema heart" are not corrected by digitalis; there is even evidence that cardiac tolerance to digitalis is reduced in myxedema. "Myxedema heart" does not exist as an isolated finding, and clinical stigmata of myxedema are invariably present in other areas before "myxedema heart" is manifest.

Plasma volume is contracted in myxedema, and velocity of blood flow is usually diminished although normal; even elevated values have been encountered. The output of the heart is invariably reduced; values approximating 50% of normal have been reported (19, 60). Systemic blood pressure is most commonly decreased. However, both systolic and diastolic hypertension may occur. Mean arterial pressure is usually normal, or even elevated and this, coupled with the low cardiac output, would indicate that total vascular resistance is increased. It has been postulated that an absolute reduction in the cross-sectional area of peripheral vascular beds (e.g., the skin, etc.) may occur.

Whether the reduced cardiovascular dynamics in myxedema are adequate for the demands of the body is still a controversial issue. In myxedema, as in many forms of congestive heart failure, the cardiac output is extremely reduced. However, in contradistinction to cardiac decompensation, peripheral venous pressure is normal, and neither pulmonary artery pressure nor right ventricular end-diastolic pressure is elevated (19). Moreover, although reports are limited, it would seem that the myxedematous subject can respond to exercise with an augmented cardiac output and that pulmonary artery pressure does not usually rise in the process, although it may (19). Arteriovenous oxygen differentials have been invoked as the classic criterion for circulatory adequacy. It is generally believed that the differences are widened when cardiac output is below the metabolic needs of the tissues.

In myxedema, interpretation of such data is difficult. The anemia and arterial unsaturation, frequent in myxedema, would tend to lower A-V differentials for oxygen; sluggish circulation in such areas as the skin would widen them. For the body as a whole, mixed arteriovenous oxygen differences are usually normal in myxedema. However, many instances of increased mixed arteriovenous oxygen differentials have been reported, thus indicating that cardiac output may be reduced to a greater extent than the integrated extraction of oxygen by the tissues. Examination of regional vascular beds has yielded variable results. For the kidney, the data would indicate that tissue metabolism, oxygen extraction and renal blood flow are reduced equally. On the other hand, for the brain, normal (60) as well as widened (61) cerebral arteriovenous oxygen differentials have been reported. It is apparent that definitive demonstration of circulatory adequacy in myxedema must await further studies, especially under conditions of exercise.

Whether myxedema exerts potentially deleterious effects on the cardiovascular system is another moot question. Analysis is complicated by the fact that myxedema is characteristically seen in an age group wherein the statistical incidence of other forms of heart disease is high. When hypertension accompanies uncomplicated myxedema, it is frequently ameliorated by therapy with thyroid extract. Similarly, cases have been cited in which angina occurred and was relieved by the restoration of eumetabolism. Angina, however, is extremely rare in myxedema, and the angina of coronary insufficiency is usually ex-

acerbated by the initiation of thyroid therapy. We can find no conclusive evidence that the hyperlipemia of myxedema promotes atherogenesis. The latter may be an entirely different problem from that of whether *established* atherosclerosis is propagated further by the aberrations in lipid metabolism occurring in myxedema.

Gastrointestinal System

The generalized retardation of body processes that occurs in myxedema extends to every aspect of gastrointestinal function. Intake of food is usually diminished commensurate with the reduced metabolic rate. Anorexia occurs in about half the cases of myxedema. Hence, the modest weight gain commonly seen in early myxedema may represent chiefly retained fluids.

Intestinal motility is retarded and thus defects in total absorption have not been demonstrated, although rates of absorption may be reduced. Constipation is prominent and may reflect the lowered food consumption, diminished peristaltic activity and consequent increase in the absorption of water. For the patient, relative changes in bowel pattern may constitute an effective index of the adequacy or failure of thyroid therapy.

Myxedematous infiltrations may occur throughout the intestinal tract, especially in the submucosal portions of the bowel wall. Hypotonia and atony of bowel may result. Megaduodenum, megacolon and fatal cases of paralytic ileus have been described. Recent reports of hypotonia of the gallbladder have appeared also.

Data on gastrointestinal secretions in hypothyroid humans are meager. Glandular elements are reduced and mucosal atrophy is prominent, especially in the stomach. Stanley, in reviewing many published reports, derives an average incidence of 42% for gastric achlorhydria in myxedema (68). Peptic ulcer is rare. The incidence is only one eleventh of that seen in general eumetabolic hospital patients. In thyroidectomized dogs, elaboration of renin and pepsin is reduced and concretions within the gallbladder are common. Hepatic dysfunction has not been reported.

Reproductive System

The role of the thyroid in obstetric and gynecologic practice

has evoked much literature but few definitive answers. An examination of the therapeutic rationale for administering thyroid in disorders of fertility and menstruation is beyond the scope of this review. However, there are distinct gonadal changes that commonly accompany clinical myxedema.

Menorrhagia occurs in one third to one half of premenopausal females with myxedema. Amenorrhea is rare. Recently, Goldsmith and co-workers used refined technics to elucidate the pathophysiology of menstrual disorders that occur in myxedema (23). They were able to demonstrate ovulatory failures in 7 of 10 patients and an inadequate effect of the corpus luteum on the endometrium in 8. Normal ovulatory cycles were present in only 2 patients. Thus, they concluded that there is an inadequate production of or ineffectiveness of the luteinizing hormone in myxedema. Other factors may be operative also. The evidence for an increased sensitivity of myxedematous tissues to estrogens has been cited previously.

In normal pregnancy, the concentrations of circulating thyroid hormone (PBI) and the TBP of plasma are elevated (18, 29). In pregnant patients with treated myxedema that we have seen, PBI has remained constant or has been increased slightly. We have measured TBP levels in 6 pregnant females with treated myxedema. In each instance, the normal TBP changes of pregnancy were present. Well-documented cases of pregnancy and of full-term deliveries in untreated myxedema patients have been reported, although these are rare.

Data on male gonadal status in human myxedema are sparse, and serial observations of sperm counts or testicular biopsies are not available. In animals, diminution of reproductive capacity in hypothyroid males varies with the species. We treated one 29-year-old male with primary myxedema in whom fertility was unimpaired, despite at least 4 years of known thyroidal failure.

Diminished libido occurs so frequently and early in the development of myxedema that this condition may furnish valuable historical data in estimating the onset of myxedema.

Muscular System

Transitory, diffuse myalgias occur frequently in myxedema and may be exacerbated by muscular exertion and by reduced environmental temperatures (paramyotonia). Initiation of vol-

untary muscular movements proceeds slowly, and hypotonia of visceral muscles in the uterus and the bladder has been reported. Muscle power is minimally, if at all, reduced. A modest increase in muscle volume may be observed. These phenomena find extreme expression in the rare Hoffmann or Kocher-Debré-Séméldigne syndromes wherein myxedema is associated with myotonoid movements and true hypertrophy of skeletal muscles. Earlier reports of mucinoid and lipoid infiltrations into muscles of hypothyroid humans have not been fully corroborated. Abnormalities of the sarcoplasm may be demonstrated in experimentally athyreotic animals.

Prolongation of deep tendon reflexes constitutes a classic physical finding in myxedematous patients. Serial observation (especially at a selected site such as the Achilles tendon) affords an excellent objective index of the efficacy of thyroid therapy. Recent investigations (42) have disclosed that conduction through the neural components of the reflex arc is unaltered in myxedema. Rather, muscular contractions as well as muscular relaxation are retarded. The thermal reductions in myxedematous muscles are insufficient to account for the magnitude of changes. Lambert and his co-workers have concluded that the defect resides within the contractile mechanism of the muscles (42). An aspect of creatine metabolism may be involved. In adults with myxedema, daily creatine output and tests of creatine tolerance are normal. However, a transient supranormal creatinuria ensues when minute amounts of thyroid extract are administered. In children, such therapeutic tests are not necessary to demonstrate abnormalities. Hypothyroid children do not exhibit the normal creatinuria of childhood; their daily excretion of creatine is much less than that of eumetabolic contemporaries.

Skeletal System

The dynamics of exchange of radioactive calcium are retarded in myxedema (38). This recent observation confirms the older reports that urinary and fecal excretions of calcium and phosphorus are reduced in hypothyroid subjects maintained on constant low-calcium diets. The effects are not mediated through the parathyroids but reflect an action of thyroid hormone chiefly exerted on endochondral rather than periosteal bone formation. In adults with myxedema, x-ray changes

are not seen, and values for serum Ca, P and alkaline phosphatase are normal. In contrast, in hypothyroid children serum phosphatase is reduced and roentgenographic aberrations are numerous. In cretins, closure of fontanelles is retarded. Resorption of deciduous teeth and eruption of permanent teeth are extremely delayed. The epiphyses show the most striking changes, and epiphyseal dysgenesis is the characteristic lesion. The orderly sequence of endochondral osteogenesis is disrupted. Cartilaginous proliferation, epiphyseal maturation and closure are affected. Ossification occurs in indistinct, scattered foci that ultimately coalesce into irregular epiphyseal ossification centers. The head of the femur and the tarsal navicular bone are involved most consistently. Eventually, skeletal maturation occurs, even in the absence of therapy. However, lack of epiphyseal union may persist into adult life in such sites as the lesser trochanter of the femur and the ischial rami of the iliac crest. Deviations in dental and osseous age from chronologic age are of great value in assessing hypothyroidism in infants after the first few months.

Hematopoietic System

Measureable abnormalities of leukocytes and platelets are uncommon in myxedema. Mild anemias, with hemoglobin concentrations of 9-11 Gm.% and red blood cell counts in the range of 3 million occur almost invariably. The uncomplicated anemia of myxedema is usually normocytic, normochromic; on occasion, macrocytosis may predominate. Elevation of the sedimentation rate may occur. In cretins, hypoplasia and fatty infiltration of the bone marrow have been reported. Hypocellularity of the marrow with preservation of normal erythroid: myeloid ratios occurs in adult myxedema. Correction of the anemia requires thyroid therapy. Whether the anemia represents yet another manifestation of the widespread reduction in protein anabolism, or whether it results from altered oxygen extractions in the areas which regulate erythropoiesis has not been clarified. The relatively slow response to thyroid therapy would favor the latter explanation.

The most common cause of severe anemia in myxedema is associated iron deficiency. Contributing factors may be the menorrhagia and the gastric achlorhydria that frequently occur. When hypothyroid patients with iron-deficiency anemia

are treated sequentially with iron and with thyroid extract, reticulocytosis follows the exhibition of each agent, thus documenting the dual nature of the etiologies (12).

Central Nervous System and Psyche

The mental torpor, lassitude, drowsiness and memory deficits in myxedema were prominently described in the 1888 report of the Committee on Myxoedema of the Clinical Society of London. The association of myxedema and psychotic episodes was also appreciated and, until therapy with thyroid extract was introduced, overt psychosis occurred in one third to one half of patients with myxedema. Since then, clinicians have been consistently impressed by the high incidence of psychic changes in thyroprivics. Lethargy, slow speech and impaired recall were present in more than two thirds of 77 patients in Lerman's series (45). Although affect is frequently flattened in hypothyroid people, Means and others have been impressed by their placidity and good humor (51). On occasion, insomnia and irritability may predominate. Most characteristically, however, somnolence and equanimity prevail. Reports of frank psychotic changes continue to appear, and the name "myxoedematous madness" has been affixed to this entity (3). The impairment of discriminative capacities in patients with early myxedema may be masked by the concurrent decline of initiative and productivity. Similarly, because of the age at which myxedema frequently develops, the mental changes may be ascribed to menopause or senility. Complete deterioration of faculties may occur terminally, with cerebration of myxedematous cachexia on a vegetative level.

Other neurologic defects may be manifest. Deafness of the middle-ear, nerve, or combined variety, is encountered in one third of the patients; two thirds complain of vertigo. Headache can be a prominent symptom in otherwise obscure cases. Peripheral paresthesias may occur, and hypothyroid patients in whom convulsive disorders were corrected by thyroid therapy have been described (51). Clinical evidence would suggest that thyroid hormone is important in neonatal cerebral development. Where athyreosis is present in infants a few months old, a 75% incidence of permanent mental deficiency ensues. However, the chances are better than 90% that normal mental development can be effected in patients with juvenile

myxedema developing after age 2. In cretinism, as well as in juvenile and adult myxedema, electroencephalographic changes consisting of low voltage, absent alpha waves and slow waves of 3-6 per second frequency are present.

The basis for these phenomena is unknown. As yet, there is no conclusive evidence that thyroid hormone acts directly on nerve tissue. Indirect effects could be mediated by an altered vascularity or an altered composition of cerebral perfusate. Characteristic changes are not seen in the brain at autopsy. The conflicting animal data on the action of thyroid hormone on the metabolism of nerve tissue have been admirably reviewed by Barker (6). Consistent enzymatic and respiratory changes in brain tissue excised from athyreotic animals have not been demonstrated. In vivo studies of myxedematous humans are equally contradictory. It has been estimated that reductions of 25-30% in cerebral oxygen consumption will produce disturbed mentation in man. Changes of this magnitude have been reported (60). However, the findings of reduced cerebral utilization of glucose and oxygen in myxedema have not been confirmed in more recent studies in which values were obtained in the same patients both before and after therapy (61).

ETIOLOGIC CLASSIFICATION

The foregoing sections have described the metabolic effects and peripheral actions of thyroid hormone and the consequences when supplies of hormone are inadequate to meet the needs of peripheral tissues. Although peripheral requirements increase in many circumstances, they do not seem to exceed the capacity of an otherwise normal gland to produce hormone. Thus, the predominant etiologic factor in the genesis of myxedema is a reduction in the glandular output of hormone. In the following section, we will attempt to categorize and characterize the various disorders which lead to the syndrome of hypothyroidism.

Hormonal insufficiency may result from insufficient glandular tissue, insufficient trophic stimulation of an otherwise normal thyroid and intrinsic or extrinsic restrictions of normal glandular mechanisms for the synthesis, storage and release of hormone. Variations in the resulting clinical picture will depend on the severity, age at onset and rapidity of de-

velopment of the hypothyroid state. Nevertheless, disorders in all three categories will share many clinical features and end-organ defects described in preceding sections. In addition, all will share a reduced concentration of active thyroid hormone in the circulation, and all will display laboratory evidence of diminished hormonal activity in the periphery.

Consistent differences between the various categories will depend on whether the function of the pituitary gland is intact and on whether the thyroidal lesion is predominantly anatomic or functional. Although the thyroid gland may be capable of a low level of autonomous function, maintenance of normal thyroidal mass and hormonal output is dependent on continued stimulation of the gland by hypophyseal thyroid-stimulating hormone (TSH). Thus, when secretion of TSH fails, thyroidal atrophy and insufficient elaboration of hormone occur. When the function of the anterior pituitary is intact, insufficiency of thyroid hormone results in augmented secretion of TSH. If the thyroidal lesion is anatomic, i.e., if the restriction in glandular mass is severe, subnormal quantities of hormone will be produced, despite intense stimulation of whatever thyroid tissue may remain. If the thyroidal disorder is functional, i.e., if the glandular lesion is biochemical, growth of the gland and goiter ensues. Goitrogenesis and augmented activity of unimpaired steps in the biosynthesis of hormone may suffice to overcome a partial functional impairment. However, as the impairment becomes progressively severe, compensatory stimulation fails, and goitrous hypothyroidism results. Goitrous hypothyroidism thus follows severe degrees of the same functional disabilities which, in milder form, are characterized by goiter alone.

Nongoitrous Hypothyroidism

Primary myxedema.—The most common and most important cause of hypothyroidism is idiopathic atrophy of the thyroid gland which, with its fully developed clinical picture, has been termed primary myxedema. Its etiology is entirely unknown. It can rarely be ascribed to pre-existing infection, inflammation or to exhaustion following prolonged hyperfunction. Prolonged inadequacy of glandular stimulation by TSH also can be excluded for several reasons. First, patients with primary myxedema do not respond to exogenous TSH as do

patients with either long-standing pituitary failure or prolonged pituitary suppression by exogenous thyroid hormone (78). Second, abnormally high titers of TSH have been found in the blood and urine of patients with primary myxedema (30).

The disease may occur at any age, but is most commonly recognized in the 40-60 group. Like most other thyroidal disorders, it is more common in females (4-7:1).

Onset is extremely insidious, so first symptoms are difficult to date. This gradual transition into the hypothyroid state probably depends on two factors: a slow, progressive thyroidal atrophy and a slow progression of symptoms and signs, even after thyroidal failure is complete. Early symptoms may include no more than apathy, weakness and easy fatigue. Women may report menstrual disturbances, especially menorrhagia. Diminution in sweating and cold intolerance also may appear early. By this time, a moderate hypometabolism is usually present. Eventually, maximal hypometabolism is achieved, but the disease picture continues its slow evolution. Distinct physical and mental retardation may appear, accompanied by integumentary changes, hoarseness, constipation and exertional dyspnea. In advanced stages, cachexia, psychosis or anemia may be present. In patients with advanced myxedema, heart failure, intercurrent infection and severe cachexia are the most frequent causes of death. Occasionally, intractable coma is the terminal event. Although the foregoing describes the typical course of progressive, severe myxedema, manifestations in a particular organ system occasionally predominate.

POSTOPERATIVE MYXEDEMA.—Postoperative myxedema most commonly follows subtotal thyroidectomy for diffuse toxic goiter. That a reduction of total glandular mass is the critical determinant for developing the disease is suggested by the observation that the incidence of postoperative myxedema is in direct proportion to the quantity of tissue removed at surgery (15). However, the thyrotoxic remnant has considerable capacity to undergo anatomic and functional regeneration, as evidenced by the occasional development of recurrent thyrotoxicity at some time after operation. Furthermore, although approximately three fourths of postoperative hypothyroidism cases will have developed during the first postoperative year, the rest may occur as late as 7 or 8 years after surgery. This delayed development of the hypothyroid state may be initiated

pothyroidism in several respects. In both circumstances, hypothyroidism usually does not become manifest for several month-

by the superimposition of a reduction in functional capacity on a diminished glandular mass.

Postoperative myxedema occurs in about 5% of patients subjected to subtotal thyroidectomy. It is most common following subtotal removal of diffusely hyperplastic, rather than toxic, adenomatous goiter and is especially frequent after secondary thyroid surgery. It may occur at any age, and is transient in approximately one third of cases. In general, late development of hypothyroidism following surgery indicates a poor prognosis for eventual recovery. Both the late appearance of hypothyroidism and its occasional remission signal the need for prolonged follow-up of surgically treated patients.

Clinical features of postoperative hypothyroidism are similar to those of primary hypothyroidism of comparable severity. In the postoperative patient, however, the physician is already alerted to the potential development of thyroidal failure. Early recognition of this entity is thus facilitated, and the diagnosis may often be made earlier than is possible in the patient with primary myxedema. Thus, the evolution of full-blown hypothyroidism and its attendant disabilities may be prevented. Postoperative follow-up should be especially searching in children, in whom retardation of physical maturation and mental activity are pronounced manifestations of the hypothyroid state. Observation of the growth curve may disclose a slowing of the slope as an early sign.

POSTIRRADIATION MYXEDEMA.—Destruction of thyroid tissue as a result of external or internal irradiation may lead to hypothyroidism of the athyreotic or hypothyreotic type. Internal irradiation by means of I^{131} has been widely used for total thyroidal ablation in patients with carcinoma of the thyroid gland or with severe cardiovascular disease and for partial destruction of the gland in patients with thyrotoxicosis. In the latter group, induction of hypothyroidism is an undesirable complication, occurring with a frequency that varies widely in reported series. Most commonly cited figures cluster around 10% (62). Although the incidence of thyroidal failure is unquestionably related to the quantity of radiation delivered to the gland, factors of individual susceptibility also seem highly important. Doses of I^{131} inadequate to induce remission in some patients may lead to the development of hypothyroidism in others.

Postirradiation hypothyroidism resembles postoperative hy-

of apparent onset may depend on the functional capacity of

pothyroidism in several respects. In both circumstances, hypothyroidism usually does not become manifest for several months following treatment, but is commonly evident within a year and in both types recovery from hypothyroidism is not uncommon. Furthermore, postirradiation myxedema may not appear until many years after treatment. In our experience, the longest interval between treatment and the onset of hypothyroidism has been 8 years.

SPORADIC CRETINISM.—Cretinism is the clinical state resulting from marked thyroidal insufficiency beginning during prenatal or neonatal life. Of the several varieties of cretinism occurring in areas other than those of endemic iodine deficiency, sporadic, nongoitrous cretinism is the most common. This results from complete atrophy or absence of the thyroid gland or from the presence of only small remnants of thyroidal tissue incapable of secreting adequate amounts of hormone.

It has been suggested that relatives of sporadic cretins demonstrate an unusually large incidence of thyroidal disease (8). On the other hand, instances of athyreotic cretinism occurring in but one of monozygotic twins would indicate that hereditary factors need not always be important in the genesis of this disease (79).

Of considerable importance is the question of whether the hypothyroid state can exist in utero. Although some transplacental passage of thyroid hormone occurs in humans, rates of transfer have not been completely assessed (28). Consequently, it cannot be stated with certainty whether, when maternal thyroidal function is normal, as is usually the case, adequate supplies of hormone will be available to the athyreotic fetus. Rarely, patients may demonstrate a level of osseous development below that of the normal newborn, together with dysgenesis of prenatal centers of ossification. These facts, together with the observation that birth weights of cretinous children may be somewhat increased, suggest that occasionally, at least, hypothyroidism may antedate birth (59).

Neonatal cretinism may be present in all degrees of severity. As the age at apparent onset increases, the clinical picture may merge imperceptibly with that of early juvenile athyreotic hypothyroidism, i.e., hypothyroidism in the young child. The two nosologic entities may, in fact, be manifestations of the same disease and the severity of symptoms and the time

of apparent onset may depend on the functional capacity of small thyroidal remnants (49).

As Wilkins (59) has emphasized, the diagnosis of hypothyroidism in infancy and childhood depends on three varieties of stigmata: functional changes, epiphyseal dysgenesis and retardation of growth. Among the functional changes noted are physical and mental lethargy, constipation and poor peripheral circulation, muscle tone and appetite. Hirsutism has recently been emphasized as a prominent finding in cretinous children. Retardation of growth is evidenced by retention of infantile nasolabial configuration and skeletal proportions, delayed and defective dental development and delayed osseous growth and maturation. Beyond the first year, when bone age in hypothyroidism may show little abnormality, assessment of the level of osseous development is a powerful tool, not only in diagnosis but also in evaluating the age at onset of the hypothyroid state and the progress of therapy.

SECONDARY OR PITUITARY MYXEDEMA.—Partial thyroidal atrophy and diminished production of hormone occur when stimulation of the thyroid by hypophyseal TSH is decreased. Instances have been reported in which reduction in the secretion of TSH has apparently been unaccompanied by other abnormalities of hypophyseal function (65). Nevertheless, secondary hypothyroidism almost always results from widespread disease of the pituitary gland or its surrounding structures. Thyroidal insufficiency thus represents but one, although perhaps a prominent, portion of the picture of anterior hypopituitarism. Hypothyroidism of this type thus takes on the characteristic age and sex incidence of the underlying hypophyseal disease.

Secondary hypothyroidism varies widely in its severity. In the evolution of the syndrome of anterior hypophyseal failure, gonadal and adrenal insufficiency frequently precede detectable diminution in thyroidal function. From this extreme, wherein thyroidal function is apparently intact, the severity of hypothyroid symptoms shades gradually to instances in which the syndrome of myxedema is the outstanding feature.

Peripheral manifestations of secondary hypothyroidism do not differ materially from those of primary hypothyroidism of comparable severity. Nevertheless, considerable importance is attached to distinguishing correctly between primary and pituitary myxedema. Treatment with thyroid hormone alone

fails to correct the pluriglandular insufficiency and may occasionally precipitate acute adrenocortical insufficiency.

Clinical features related to the origin of the hypopituitarism may aid in differentiating between primary and secondary myxedema. In almost all cases of anterior hypophyseal insufficiency, the origin is either tumor of the pituitary gland or the circumsellar region or postpartum necrosis of the anterior pituitary gland (Sheehan's syndrome). Cases associated with tumor commonly display headache, visual defects and, occasionally, nausea and vomiting. Alterations in the architecture of the sella turcica, such as sellar enlargement, destruction of the clinoid processes, or both, are manifest in x-rays of the skull. Up to age 30, tumors are most commonly craniopharyngiomata (suprasellar cysts), of which approximately 75% display calcification on x-ray. Tumors causing pituitary insufficiency in later life are most commonly chromophobic adenomata.

Hypopituitarism following postpartum hemorrhage manifests, in addition to the initial bleeding episode, rapid disappearance of breast milk or complete failure to lactate, persistent amenorrhea, loss of hair, especially in the axillae and groin, and loss of libido.

Abnormalities in adrenal and gonadal function which may occur in primary myxedema, as described earlier, may occasionally create confusion in differentiating this disease from secondary myxedema. Specific laboratory procedures, often of great aid in this regard, will be discussed below.

Goitrous Hypothyroidism

The foregoing types of hypothyroidism result either from an inadequate quantity of functioning thyroid tissue or from inadequate stimulation of a potentially normal thyroid gland. These disorders should merit the designation "hypothyroid states." In the diseases that follow, hypothyroidism results either from nutritional or pharmacologic factors that impede the formation of hormone or from inherent biochemical abnormalities within the gland. As a group, disorders of this type are generally characterized by goiter, and much less often by clinical hypothyroidism. Although they account for far fewer cases of clinical hypothyroidism than do the types already discussed, they provide fascinating challenges to pathophysiologic

interpretation. A consideration of these diseases, necessarily brief in a review of this scope, is best projected against a background of the biosynthetic stages that comprise the normal mechanisms for hormonal synthesis, storage and release.

Synthesis of hormone can be considered to occur in 3 stages. First, the thyroid gland actively concentrates inorganic iodide from the extracellular fluid. This energy-dependent "iodide trap" provides concentrated substrate for subsequent steps in hormonal synthesis. Next, oxidation of trapped iodide occurs and the elemental iodine which presumably results iodinates tyrosyl residues within the thyroglobulin molecule. The resulting mono- and diiodotyrosine undergo oxidative coupling to yield iodinated thyronine derivatives, such as thyroxin and triiodothyronine. These iodinated organic compounds are bound within the thyroglobulin molecule and stored within the follicular lumen. Proteolysis of thyroglobulin liberates the iodinated amino acids and makes possible their passage into the circulatory system. However, only iodothyronines normally reach the circulation. Mono- and diiodotyrosine are deiodinated by glandular dehalogenases, and the iodide thereby liberated is then available for reincorporation into hormone.

IODINE DEFICIENCY.—In man, dietary iodine is apportioned between the thyroid gland and the urine according to the capacities of the gland and the kidneys to remove inorganic iodide from the blood. Under conditions of normal dietary intake, adequate iodine is available for the synthesis of hormone, if the thyroid accumulates approximately one third of the iodide entering the metabolic pool. Under conditions of dietary iodine deficiency, a much larger fraction of available iodine must be accumulated if hormonal requirements are to be met. This can usually be accomplished by an increase in glandular mass and in unit functional capacity. Thus, a eumetabolic state is maintained, but only at the expense of goitrogenesis (iodine deficient or simple goiter). When restriction in dietary iodine is severe, compensatory anatomic and biochemical hyperplasia may be insufficient to permit the synthesis of normal quantities of hormone. The hypothyroidism which then results is rare, but, except for the presence of goiter, resembles athyreotic hypothyroidism in all respects.

Neonatal hypothyroidism may occur in offspring of patients with severe iodine deficiency, manifested by goiter or hypothyroidism. Cretins of this type (endemic cretins) most often

display goiter. However, nongoitrous cretins are occasionally seen in areas of endemic iodine deficiency. In such patients, the thyroid is considered to have undergone exhaustion atrophy.

There is suggestive evidence that constitutional or thyroidal factors may condition the extent of goitrogenesis and impairment of hormonal synthesis seen in areas of endemic iodine deficiency. First, even in areas of endemic deficiency, goitrogenesis is not invariable. Second, a wide variation is seen in the severity of endemic neonatal hypothyroidism, even in members of the same family. Hypothyroidism, secondary to severe iodine deficiency in either infants or adults, is now virtually unknown in the United States. An extensive review of endemic iodine deficiency has recently been presented by Stanbury and his co-workers (66).

DIETARY GOITROGENS.—A variety of foods contain substances that interfere with the capacity of the thyroid gland to accumulate iodine and to synthesize hormone. In man, the most potent foods belong to the Brassica family. These include rutabaga, cabbage, turnips, kale, rape and mustard. A potent thyroid-blocking agent, L-5-vinyl-2-thiooxazolidone, has been isolated from rutabaga (4). Laboratory studies in man indicate that goitrogenesis would require the ingestion of larger quantities of vegetables than are in the usual diet. Recent evidence, however, indicates that the potent goitrogen agents may appear in the milk of cattle eating fodder of this variety. Milk-borne transmission of antithyroid agents has been convincingly implicated in the pathogenesis of endemic goiter in Tasmania (13).

Although well-documented cases of hypothyroidism due to the ingestion of dietary goitrogens are lacking, these agents may be among factors conditioning or exaggerating the response to iodine deficiency or other exogenous or endogenous stimuli to goiter formation.

PHARMACOLOGIC AGENTS (5).—Thiocyanate, perchlorate, nitrate and certain other monovalent anions interfere with the first step in hormonal biosynthesis, i.e., the active concentration by the thyroid gland of inorganic iodide. Blockade of the "iodide trap," leading to goitrous hypothyroidism was occasionally seen when thiocyanate was widely used in treating hypertension. It is evident that thiocyanate goiter should be alleviated by iodides.

The more commonly used antithyroid drugs, notably those of the thiourea and mercaptoimidazole series, impair hormonal synthesis by inhibiting the oxidation and organic binding of iodine within the gland. Therapeutic doses effect only a partial inhibition. However, with large doses, virtually complete inhibition of hormonal synthesis can be achieved. Therefore, hypothyroidism can be induced by overly vigorous therapy of thyrotoxicosis. This may be difficult to recognize in its early stages. However, diagnostic advantage may be taken of the observation that in most cases of thyrotoxicosis, the thyroid gland will remain constant or become smaller during treatment. The appearance of enlarging goiter during therapy, often with a bruit or thrill, frequently signals overtreatment.

Para-aminosalicylate in doses commonly used to treat tuberculosis, and resorcinol used as a cutaneous antiseptic have been shown capable of inducing goitrous hypothyroidism. Like the therapeutic antithyroid drugs just described, they inhibit thyroidal organic iodinations.

Paradoxically, in rare instances, iodine may act as a goitrogen. This entity of iodide goiter, only recently recognized, has most often appeared in patients receiving iodine in pharmacologic doses. The precise pathogenetic mechanisms are unknown. However, in animals, as well as in normal and thyrotoxic humans, large quantities of iodine diminish the production of thyroid hormone by inhibiting the organification of thyroidal iodide. In animals, this effect is transient, but its duration in humans is unknown.

To date, approximately 20 cases of iodide myxedema and goiter have been reported in adults. However, babies whose mothers have received large doses of iodides frequently demonstrate neonatal goiter and transient hypothyroidism. The fact that iodide goiter is more frequent in the newborn than in adults is perhaps explained by recent observations that the fetal plasma contains iodide several times more concentrated than that in the maternal circulation. The extreme rarity of this disease in adults suggests that the thyroid gland of iodide goiter may harbor an underlying abnormality, making it unusually susceptible to the inhibitory action of iodides. We have recently observed one patient with iodide goiter in whom relief of goiter and restoration of a eumetabolic state after withdrawal of iodides was followed within several months by the onset of spontaneous myxedema.

Goiter and hypothyroidism in patients receiving cobalt as a hematinic agent has recently been described (39). The underlying mechanism is unknown.

INBORN ERRORS IN METABOLISM OF IODINE (67).—Recently a number of apparently inborn, and often familial, abnormalities in the thyroidal metabolism of iodine have been described. All are associated with goitrogenesis, which at times may be extreme. Three varieties have been reported to date. In the first, failure of hormonal biosynthesis results from an inability of the thyroid gland to organify ionic iodide. In the second category, iodotyrosines are not coupled to form the hormonally potent iodothyronines (thyroxin and triiodothyronine). The third variety of intrinsic abnormality results from an inability of the thyroid gland, and perhaps of peripheral tissues, to deiodinate the iodotyrosines. In this group, the deiodinating enzymes that normally prevent the appearance of mono- and diiodotyrosine in the circulation are defective or absent. Consequently, large quantities of mono- and diiodotyrosine are found in the blood and urine. Some thyroxin is formed in the gland and released into the circulation. The precise reasons for goitrogenesis have not been clarified.

In recognized instances, such abnormalities appear in early neonatal life, and therefore give rise to cretinism. These diseases thus comprise the second variety of nonendemic cretinism—goitrous cretinism. Multiple cases are frequently seen in siblings.

Most likely milder forms of similar or related biochemical abnormalities may occur in adults and may cause a number of instances of sporadic nontoxic goiter.

HASHIMOTO'S STRUMA (STRUMA LYMPHOMATOSA).—Probably the most common cause of goitrous hypothyroidism is Hashimoto's struma, or lymphadenoid goiter. This disease, seen almost exclusively in females, may occur at any age but is most frequently diagnosed in patients between 40 and 50. Although the ultimate etiology of Hashimoto's disease is unknown, recent observations provide important clues to an understanding of the pathologic physiology of this disorder. Following the administration of tracer doses of I^{131} to patients with Hashimoto's disease, there appears in the serum protein-precipitable radioactivity, a portion of which does not display the solubility characteristics of thyroxin and triiodothyronine (54). This unusual iodinated moiety seems to be not an

iodinated amino acid, but rather an iodoprotein, perhaps thyroglobulin. More recent observations indicate that antibodies against human thyroglobulin may be found in the serum of patients with Hashimoto's disease (17). Presumably, therefore, an initiating, unknown factor leads to escape of thyroglobulin from within the follicular cavity. This protein, having escaped from its normal site of sequestration, is capable of inducing an auto-immune response. Antibodies formed either at distant sites or perhaps in lymphocytic aggregates within the interstitium of the gland itself then may react with intrafollicular thyroglobulin and induce inflammatory reactions leading to further follicular destruction.

In Hashimoto's struma, inadequate production of normal hormone may result, therefore, from reduced functioning of glandular mass, and also from passage of the noncalorigenic protein, thyroglobulin, into the circulation. Mild or moderate hypothyroidism is common in patients with this disease, and full-blown myxedema is occasionally seen. Of considerable interest is the observation that frank myxedema develops with unusual frequency in patients with Hashimoto's disease whose thyroid glands have been subjected to operative trauma. Not only subtotal thyroidectomy, but also simple transcision of the thyroidal isthmus may trigger thyroidal failure. It is tempting to speculate that operative manipulation of the thyroid gland, with its attendant release of thyroglobulin into the circulation, evokes a booster antibody response, thereby initiating rapid destruction of glandular tissue.

LABORATORY FINDINGS

All varieties of hypothyroidism share abnormalities with a number of commonly used laboratory tests. The first and most important finding common to all is a decrease in the circulating concentration of active thyroid hormone. This is generally measured as the protein-bound iodine (PBI) but, under circumstances in which abnormal iodinated products appear in the serum, is best measured as the butanol-extractable iodine (BEI). Other laboratory abnormalities that reflect the inadequacy of the hormonal supply to peripheral tissues are common to all types of hypothyroidism. These include lowered basal metabolic rate and increased serum cholesterol.

Major types of hypothyroidism differ according to varia-

tions in the thyroid gland activity. Of the common tests, only those using radioactive iodine directly assess thyroidal activity. The procedures most commonly used measure thyroidal uptake or urinary excretion of a tracer dose of I^{131} and estimate the concentration of hormonal (precipitable) radioiodine in the serum at a given time following the dose. Since inorganic iodide is distributed between the thyroid and the kidney, the thyroidal uptake and the urinary excretion of I^{131} are reciprocally related and reflect thyroidal iodine-accumulative capacity. They do not, of course, reveal the chemical nature of the iodine once it has accumulated in the gland. On the other hand, measurements of the protein-bound I^{131} are largely a reflection of the rate of turnover, or release, of glandular hormone.

In athyreotic hypothyroidism, both thyroidal uptake of I^{131} and the rate of appearance of labeled hormone in the serum are markedly decreased. In instances of hypothyreotic hypothyroidism in which surviving thyroidal remnants are intensely stimulated and hyperfunctioning, thyroidal uptake of I^{131} is also subnormal, but values of the PBI^{131} are often in the normal or thyrotoxic range, since the turnover of iodine in such remnants is rapid.

In pituitary myxedema, a low rate of hormonal biosynthesis is often preserved. This residual function, together with delayed excretion of iodide by the kidney, makes possible accumulation of quantities of I^{131} which often approach the lower limit of the normal range. Reduced turnover of glandular iodine results in subnormal values for the PBI^{131}.

In dietary iodine deficiency, thyroidal accumulation and turnover of iodine are accelerated. Radioiodine uptake and PBI^{131} in the serum are therefore in the hyperfunctioning range.

Before complete thyroidal failure, patients with Hashimoto's disease often demonstrate normal or increased thyroidal uptake of I^{131}, despite clinical hypothyroidism. Values of the PBI^{131} also may be increased. Here, however, the PBI^{131} is partially composed of iodinated moieties that exhibit the solubility characteristics of thyroglobulin. Therefore, values of the BEI^{131} which more accurately reflect the active (thyronine-like) iodinated moieties may be considerably less. Similar large discrepancies between protein-bound and butanol-extractable stable iodine (I^{127}) are occasionally seen in this disease (26).

In goitrous hypothyroidism due to intrinsically or extrinsically determined abnormalities in the thyroidal metabolism of iodine, variation in the chemical nature and the rate of turnover of accumulated I^{131} often make the commonly performed tests using radioiodine diagnostically confusing. In this category, radioactive iodine would seem more valuable as an adjunct in elucidating pathologic physiology than as a diagnostic aid.

CLINICAL USE OF THYROID-STIMULATING HORMONE

Thyroid-stimulating hormone augments both the rate of synthesis and the rate of release of hormone by the normally responsive thyroid gland. Increase in the rate of hormonal synthesis is demonstrable by such tests as the uptake of I^{131} that reflect the thyroidal avidity for iodine. Increase in the rate of release of hormone is reflected in augmented concentration of hormone in the circulation. Following short-term administration of TSH, the additional hormone released is comprised mainly of preformed rather than newly synthesized compounds.

The capacity of TSH to produce marked alterations in thyroidal function has served as the basis for increased use of this hormone in diagnosing many diverse disorders.

Differentiation of Thyroidal and Pituitary Myxedema

A number of laboratory tests aid in the differentiation of thyroidal and pituitary myxedema (78). Thus, serum cholesterol is frequently within the normal range in patients with hypophyseal disease. Estimations of urinary excretion of gonadotrophin, negligible to absent in patients with hypopituitarism, are also valuable, especially in postmenopausal women. Among more discriminating tests is the assessment of thyroidal response to TSH. One would anticipate that athyreotic hypothyroidism, or hypothyreotic hypothyroidism in which glandular remnants were already maximally stimulated by endogenous TSH, would demonstrate no response to the exogenous hormone. On the other hand, the thyroid gland of pituitary myxedema would be expected to respond, unless complete thyroidal atrophy had followed prolonged, severe hypophyseal insufficiency. Clinically, these expectations have

been borne out. Increase in I^{131} uptake following exogenous TSH has provided valuable means of differentiating secondary from other types of nongoitrous hypothyroidism. The effect of TSH on thyroidal release mechanisms, as adjudged by increase in PBI, is often less well defined, since stores of preformed hormone are depleted during long-standing hypophyseal insufficiency.

Diagnosis of Hypothyroidism in the Treated Patient

It is often desirable to ascertain the accuracy of the diagnosis of hypothyroidism in a patient already receiving adequate therapy. Frequently, it is inconvenient and undesirable to observe clinical and laboratory effects which might ensue after treatment has ended. Treated patients with athyreotic or hypothyreotic hypothyroidism should respond little, if at all, to the administration of TSH. On the other hand, normal persons receiving exogenous thyroid hormone will demonstrate suppression of thyroidal uptake of radioiodine as a result of decreased elaboration of endogenous TSH. Such patients should respond to exogenous TSH similarly as do patients with true pituitary hypofunction, just described.

Diagnosis of Hypothyroidism in Patients Receiving Iodide

Iodine ingested as medication or received by the patient in the form of iodinated organic dyes during x-ray studies may depress the thyroidal uptake of I^{131} and increase the concentration of PBI in the serum for variable and often long periods. Under these conditions, the value of such tests in the patient with suspected hypothyroidism is vitiated. However, demonstration of an increase in PBI, and less often an increase in I^{131} uptake, following administration of TSH, may serve to exclude the diagnosis of athyreotic or hypothyreotic hypothyroidism.

Diagnosis of Decreased Thyroid Reserve

Recently a group of patients has been described with symptoms of mild hypothyroidism whose initial laboratory tests of thyroidal status, with the occasional exception of the serum

cholesterol, are normal. These patients, however, respond abnormally to exogenous TSH, with failure to increase the I^{131} uptake, the PBI, or both. This disorder, termed "decreased thyroid reserve," is most commonly seen in patients whose thyroid gland has been partially destroyed by surgery, radiation or inflammation (35). If untreated, some patients in this category will develop frank myxedema. However, symptoms respond well to small doses of desiccated thyroid substance. This therapeutic response differentiates such patients from a less clearly defined category of hypometabolic persons who allegedly resist treatment with thyroxin or desiccated thyroid but who respond well to triiodothyronine (40) (see Metabolic Insufficiency, p. 42).

TREATMENT

Virtually no other chronic disease can be treated as easily and as adequately as adult myxedema. Within the framework of present knowledge, complete hormonal replacement can be effected by inexpensive oral medication. There are available several therapeutic agents that seem to reverse completely the physiologic aberrations of hypothyroidism. Regardless of the agent chosen, the aim of therapy is restoration of a metabolically normal state. Although laboratory procedures may be helpful in this effort, observation of the patient affords the best means for evaluating treatment. However, in our experience, even clinical appraisal may be misleading. Frequently, small increases in the hormone dosage will result in a distinct improvement in patients already cleared of all objective evidence of myxedema. Occasionally, treatment of myxedema may unmask and evoke symptoms of latent angina pectoris, congestive heart failure or peripheral vascular disease. In such cases, it may be necessary to maintain the patient on doses which are suboptimal in other respects. In short, the therapeutic regimen should consist, as Means has suggested, of "the minimum dose that will accomplish . . . maximum possible well-being" (51).

Several characteristics of the hypothyroid patient's response to specific therapy can be understood best in relation to the kinetics of thyroxin metabolism. It has commonly been stated that myxedematous patients are inordinately sensitive to exogenous thyroid hormone. Recent studies have indicated

that while this may be true when patients are still in the hypometabolic state, it no longer pertains once they have been returned to a condition of clinical eumetabolism (24). This finding has been confirmed by studies of daily degradation of thyroxin in normal subjects and in patients with treated myxedema. These studies revealed that the quantity of hormonal iodine utilized by patients with treated myxedema, maintained in the eumetabolic state, was the same as that utilized by normal patients, i.e., 50-60 μg. of hormonal iodine daily (34). Thus, at comparable metabolic levels, the peripheral requirements for hormone were the same for patients with myxedema as for normal patients. The data further revealed that approximately 20 μg. of hormonal iodine was provided per grain of desiccated thyroid ingested. Thus, 2 or 3 grains daily would provide a quantity of hormonal iodine equal to average normal daily requirements (34).

The second characteristic of patients with treated myxedema is their ability to interrupt treatment for a moderate period without thereby producing clinical symptoms. In this regard, the patient with myxedema differs markedly from the diabetic or the addisonian. This can be ascribed to differences in the rates of disappearance of the respective hormones from the plasma. Whereas that of insulin and adrenocortical steroids is rapid, removal of thyroxin from the plasma is relatively slow. Complete cessation of therapy is associated with only a slow decrease in the plasma's PBI. Thyroxin contained in the plasma and extracellular fluid thus acts as a reservoir providing stability during lapses in therapy or under conditions that may acutely increase hormonal requirements. Therefore, restoration of the integrity of this large hormonal pool should also be an objective of therapy.

Among the available therapeutic agents whose effects have been well characterized are desiccated thyroid, L-thyroxin and L-triiodothyronine. Earlier disadvantages to the use of desiccated thyroid substance, arising from variation in potency, have now been overcome largely by standardizing the preparation according to iodine content and to physiologic activity. Purified thyroxin has both potential advantages and disadvantages. Although it makes possible administration of constant reproducible doses of a single therapeutic agent, treatment with thyroxin alone may not provide other iodinated materials, such as triiodothyronine, known to be present in whole

thyroid extract. The observation that the PBIs of patients maintained at eumetabolic levels on L-thyroxin tend to be higher than normal lends weight to this consideration.

L-triiodothyronine is a highly potent, rapidly acting agent capable of reversing all the stigmata of hypothyroidism (63). We do not recommend its regular use in treating this disease. As noted earlier, triiodothyronine is widely distributed in the body and is rapidly metabolized. As a result of these characteristics, and because its effective dose is relatively small, PBIs of patients restored to eumetabolism with triiodothyronine remain in the myxedema range. In contrast to the large and slowly metabolized pool of hormone available to the patient treated with desiccated thyroid or thyroxin, the hormonal reservoir with triiodothyronine remains small and disappears rapidly. Thus, the margin of safety in replacement therapy is narrowed.

It seems likely, however, that triiodothyronine has therapeutic value in cases in which rapid relief of myxedema is mandatory. For example, it may be valuable in treating myxedema coma. It is also established that patients with untreated myxedema cannot withstand narcotics, sedatives and sympathetic blocking agents. In acute surgical emergencies or other situations in which such agents must be used, acute restoration of eumetabolism also may be indicated.

In general, rapid relief of myxedema is to be avoided. The hazard of provoking thrombosis or acute myocardial or coronary insufficiency, especially in older patients, dictates a gradual increase in therapeutic regimen. Generally, we initiate therapy with ½ grain of desiccated thyroid, USP, and increase the dose ½ grain weekly until optimal dosage is achieved. If L-thyroxin is used, an equivalent of 100 μg./gr. of desiccated thyroid may be assumed.

Unfortunately, treatment is often less satisfactory in cretinism and in early juvenile than in adult forms of myxedema. Here, in addition to alleviating the usual functional stigmata of hypothyroidism, therapeutic objectives include restoring normal physical and mental development. Since ultimate prognosis in this regard is largely dependent on age at the onset and the duration of hypothyroidism, the importance of early diagnosis cannot be overemphasized. During therapy, all modalities of evaluation should be used, including clinical appraisal and objective measurements of progress regarding increase in height, weight, bone age and mental performance.

Laboratory aids should be used, of which measurement of the PBI or BEI are most valuable. It is especially important to remember that in athyreotic patients maintained in a eumetabolic state by the administration of desiccated thyroid, or especially thyroxin, the PBI may be above the normal range for normal persons with functioning thyroids. Rigid recommendations for dosage cannot be made. In general, however, hormonal requirements of children in relation to body size seem considerably greater than those of adults.

METABOLIC INSUFFICIENCY

The foregoing sections have described the pathophysiology, diagnosis and treatment of disease states characterized by insufficient supply of active thyroid hormone and generally recognized to be thyroidal in origin. In addition to patients with these disorders, a large number of people demonstrate hypometabolism that apparently does not originate in the thyroid. Such patients may present a wide variety of symptoms. Some of the symptoms which have been ascribed to hypometabolism are easy fatigability, somnolence, decreased mental alertness, irritability, sensitivity to cold, lassitude, easy weight gain, muscle and joint stiffness, headache, chronic constipation, amenorrhea and premenstrual tension. Associated objective signs have been described as dry skin and hair, brittle nails, muscle tenderness, anovulatory basal body temperature, oligospermia, facial puffiness, edema, water retention and obesity.

Whether the findings in such patients stem from one or more distinct disease entities has long been the subject of debate. Similar symptoms are not invariable in patients with comparably low BMRs, but may be seen in patients with normal metabolic rates. In addition, one or more of the symptoms listed may be found in patients with a variety of other well-defined diseases.

Recently, data have been presented purporting to separate from this large hypometabolic category a new entity, variously entitled "metabolic insufficiency," "nonmyxedematous, or euthyroid hypometabolism" (40, 77). Pathophysiologic definition of this proposed category has been based on two groups of findings. First, except for occasional increases in serum cholesterol, this type of patient generally demonstrates no abnormalities in the commonly used tests of thyroidal

status. Second, it has been reported that although such patients respond poorly, if at all, to the administration of desiccated thyroid or thyroxin, increase in BMR and improvement in symptomatology regularly follow the administration of triiodothyronine, either alone or in combination with thyroxin. In accord with these observations, it has been postulated that these patients with "nonmyxedematous hypometabolism" have no underlying abnormality in thyroidal function, but rather fail to respond normally to the thyroid hormone (presumably thyroxin) which their own gland provides. More specifically, it has been suggested that there exists in such patients a peripheral defect in the conversion of thyroxin to a tissue-active form of the hormone, viz., triiodothyronine.

Data obtained during studies of the peripheral turnover of I^{131}-labeled thyroxin in hypometabolic patients have been advanced in support of the foregoing hypothesis. These have consisted of an occasional and variable retardation in the fractional rate of turnover of labeled hormone (41).

However, there is some question as to whether the findings to date are sufficient to validate the theory proposed. First, although the circulating hormonal iodine in patients with "metabolic insufficiency" is assumed to be normal in type, its precise chemical nature has never been defined by any of the several technics now available for this purpose.

Second, one must consider the basic assumption that thyroxin requires conversion to triiodothyroxine to exert its metabolic action. As noted earlier, there are no data available indicating that this is necessarily the case.

Third, there is no doubt that triiodothyronine is a hormone whose potent rapid action far exceeds that of thyroxin. During attempts to induce *thyrotoxicosis medicamentosa* in normal persons, we have noted considerable difficulty both in elevating the BMR and inducing symptoms when the hormone used was either desiccated thyroid or thyroxin. In contrast, *thyrotoxicosis factitia* could be induced readily by much smaller doses of triiodothyronine. It therefore remains to be determined whether greater responsiveness to triiodothyronine than to desiccated thyroid or thyroxin is a characteristic of the hypometabolic patient or a characteristic of the hormones used.

Fourth, there are alternative interpretations of the recent demonstration that occasional subjects with "metabolic insufficiency" may manifest a retarded rate of disappearance of

thyroxin from the plasma. Several lines of evidence indicate that the rate of turnover of labeled thyroxin may be governed partly by the metabolic rate per se. Thus, accelerated disappearance of thyroxin is seen in untreated Graves' disease (34), as well as in *thyrotoxicosis medicamentosa* induced by thyroxin or triiodothyronine. Extrathyroidal causes of hypermetabolism, such as fever or leukemia, are also associated with augmentation of thyroxin turnover (70). However, extension of our original observations to larger numbers of patients with thyroidal myxedema has revealed a significant retardation of thyroxin turnover. This is reversed by administration of desiccated thyroid and correction of the hypometabolic state. Thus, it seems possible that the retardation of thyroxin turnover occasionally seen in patients with "metabolic insufficiency" is the result rather than the origin of their hypometabolism.

Central to the entire hypothesis of physiologic abnormality in "metabolic insufficiency" is the suggestion that in this syndrome peripheral tissues are unable to convert thyroxin to a metabolically active derivative, probably triiodothyronine. Therefore, it is important to examine possible physiologic consequences of a derangement of this type.

In studies of the peripheral turnover of thyroxin in hypometabolic patients just noted, the mean quantity of hormonal iodine degraded daily in the hypometabolic group was virtually identical with comparable values obtained in normal persons in the same study and in earlier studies using the same method (41, 34). While it may be granted that equal values for total daily degradation of thyroxin in normal and hypometabolic groups do not necessarily indicate that degradation in the two groups is proceeding along the same metabolic pathways, one would expect that a widespread defect in deiodination in the hypometabolic group would be associated with a diminution in the total quantity of hormone consumed.

Attention should also be directed toward the serum cholesterol in these patients, which is commonly normal. Barring gross abnormal ties in diet or in lipid metabolism, the concentration of cholesterol in serum is an indicator not of the level of activity of the thyroid gland per se but of the metabolic impact of thyroid hormone at the tissue level. Thus a normal serum cholesterol would be unexpected if, in fact, the metabolic activity of the circulating thyroid hormone were

decreased. This apparent paradox might be clarified by measurement of other indices of the metabolic action of thyroid hormone, such as the concentration in the serum of alpha-tocopherol and beta-carotene.

Finally, the postulated abnormality in patients with "metabolic insufficiency" must be viewed in the light of current concepts of the function of the thyropituitary axis. It seems likely that the ability of the circulating thyroid hormone to limit hypophyseal secretion of TSH, and thereby to regulate the activity of the thyroid gland, is dependent on the metabolic action of the hormone in the pituitary gland or hypothalamic centers. Accordingly, if thyroxin were indeed relatively inert in patients with "metabolic insufficiency," it should, like other calorigenically impotent products (e.g., diiodotyrosine), display an absolute or relative inability to suppress the thyroidal uptake of radioactive iodine. Apparently, these important physiologic data have not yet been obtained.

Furthermore, failure of thyroxin to perform its metabolic function should initiate the same chain of compensatory sequelae that has just been outlined for thyroidal diseases in which a calorigenically impotent hormone is secreted. As a result of hypophyseal activation, there should occur goiter, glandular hyperfunction and an increased rate of secretion of the glandular product. In patients with "metabolic insufficiency," none of these sequelae occurs. Thus, the proposed peripheral defect seems inadequate to explain the entire syndrome, and one must perforce postulate an additional defect in one or both members of the thyropituitary axis.

The basal metabolic rate is affected by a number of factors (both humoral and nonhumoral) other than the supply of thyroid hormone. At present, evidence seems inadequate to demonstrate that abnormalities related to the supply or metabolism of thyroid hormone are responsible for the type of hypometabolism under discussion. We hold no intrinsic bias against the concept that disorders of the peripheral metabolism of thyroxin may induce a "peripheral hypothyroidism." Strong evidence that this may sometimes be the case is provided by the recent report of a thyroid-resistant cretin who responded to the administration of triiodothyronine (33). Further, the problem may devolve on the demonstration that specific metabolic products of thyroxin are especially active

in bringing about particular metabolic actions of the hormone. Nevertheless, at present we cannot recommend widespread use of triiodothyronine for treating this ill-defined syndrome. The protean nature of the symptomatology, its broad overlap with symptoms of other organic and psychogenic disorders, the potential cardiac hazards surrounding the use of a powerful hormone, the considerable possibility of developing profound psychic dependence on the drug and the as yet ill-defined effects of prolonged thyroidal suppression suggest to us that restraint in therapy be used until the entity, if such it is, rests on firmer physiologic and diagnostic grounds.

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